



Correlation of Matrix Metalloproteinase-9 and Tissue Inhibitor Matrix Metalloproteinase-1 on Lactate Concentration in Sepsis patients Admitted to Intensive Care Unit

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Abstract

BACKGROUND: Lactate level has been used not only as a biomarker for diagnosis and guiding treatment of sepsis but also as predictor of poor clinical outcomes. Elevated lactate does not specifically reflect cellular damage and this condition can be seen in other metabolic disorders. Matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) are two new promising biomarkers that have been reported to elevate significantly in sepsis. These two biomarkers can reflect physiological changes in tissue and cellular levels.

AIM: This study aims to identify the correlation of MMP-9, TIMP-1, and MMP-9/TIMP-1 on lactate levels in sepsis patients.

METHODS: This was a cross-sectional study conducted in two hospitals, Adam Malik General Hospital, Medan, and Grand Medistra Hospital, Deli Serdang, between April 2020 and May 2021. The inclusion criteria in this study were adult sepsis patients who were admitted to ICU, with Sequential Organ Failure Assessment (SOFA) or quick SOFA score ≥ 2 . We recorded the characteristics, MMP-9, TIMP-1, and lactate concentration before given any intervention. The data were then analyzed to find the correlation.

RESULTS: Sixty-four patients were included in this study which consisted of almost equal men and women. The mean age of the subjects was 52.16 ± 16.25 years old. There was no correlation between MMP-9 and TIMP-1 toward lactate concentration ($p = 0.466$ and $p = 0.65$, respectively).

CONCLUSION: Our study showed no correlation between MMP-9 and TIMP-1 toward lactate concentration.

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Introduction

Lactate has been a very significant component in diagnosing and treating sepsis. In fact, measuring lactate level is the first step according to the surviving sepsis campaign (SSC) hour-1 sepsis bundle [1]. Lactate is known to be a useful endpoint of sepsis resuscitation [2]. However, the elevation of lactate does not specifically reflect cellular damage. Elevated lactate level can be seen in various conditions such as metabolic disorder, liver dysfunction, trauma, burns, and consumption of certain drugs [3].

Matrix metalloproteinase-9 (MMP-9) is a type of proteinase that is released during inflammation. MMP has the potential to degrade extracellular matrix (ECM) while tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) plays a role in remodeling ECM by specifically regulating activity of MMP-9 [4], [5]. MMP-9 and TIMP-1 are two promising biomarkers that have been reported to be significantly elevated and associated with severity and outcome of sepsis [6], [7]. Elevation of these biomarkers and its

ratio was found to be significantly increased in non-surviving sepsis patients [8], [9]. MMP-9 and TIMP-1 are more feasible to measure and they can describe changes in tissue and cellular levels.

Our objectives of this study were to identify the correlation of MMP-9, TIMP-1, and MMP-9/TIMP-1 ratio on lactate levels in sepsis patients.

Methods

This cross-sectional study was conducted in two hospitals: ICU of Haji Adam Malik General Hospital, Medan, and Grand Medistra Hospital, Deli Serdang, from April 2020 to May 2021. Adults ICU patients (>18 years old) with sepsis and SOFA or qSOFA score ≥ 2 were enrolled in this study. Basic demographic data, MMP-9, TIMP-1, MMP-9/TIMP-1 ratio, and lactate concentration were recorded before given any intervention. Normally distributed quantitative variables were expressed as mean and standard deviation while skewed data were

expressed as median and range. Categorical data were described as absolute count and percentage. The data were analyzed using SPSS version 26.0.

This study had been approved by Ethics Committee of Universitas Sumatera Utara.

Results

Sixty-four patients were enrolled in this study consisted of 31 men and 33 women. The baseline characteristics of subjects are shown in Table 1. Normality test was performed and the only normally distributed data were ratio of MMP-9/TIMP-1.

Table 1: Baseline characteristics of subjects

Characteristics	Value
Mean age (SD), years	52.15 (16.25)
Sex, n (%)	
Male	31 (48.4%)
Female	33 (51.6%)
Median of MMP-9 (min-max), ng/mL	1279.42 (129.23–2139.2)
Median of TIMP-1 (min-max), ng/mL	568.6 (195.2–1415.86)
Mean ratio of MMP-9/TIMP-1 (SD)	2.15 (1.18)
Median of lactate (min-max), mmol/L	1.95 (0.7–9.7)

Table 2 described the correlation test of all variables and we found no correlation between MMP-9, TIMP-1, and ratio of MMP-9/TIMP-1 toward lactate concentration ($p = 0.466$ and $p = 0.65$, respectively).

Table 2: Correlation of MMP-9, TIMP-1, and MMP-9/TIMP-1 on lactate concentration

Variables	p value
MMP-9 and lactate	0.466
TIMP-1 and lactate	0.65
Ratio of MMP-9/TIMP-1 and lactate	0.847

Discussion

Measurement of lactate concentration has been the first step of SSC bundle since 2004 [10]. However, elevation of lactate concentration is associated with many circumstances [3]. All type of shocks (not only septic shock) cause hypoperfusion and tissue hypoxia resulting in anaerobic metabolism and lactate elevation [11], [12]. In addition, it may be caused by excessive muscle activity, trauma, burns and smoke inhalation, diabetic ketoacidosis, malignancy, liver dysfunction, and metformin use [3]. These are the reasons why lactate is not appropriate to be measured in all conditions.

To date, there was no published guideline about the reference range of MMP-9, TIMP-1, and its ratio. A study in 2016 has found the reference range of MMP-9 in 1250 healthy patients to be

14.3–99.5 ng/ml [13]. According to multiple studies, MMP-9 and TIMP-1 are highly elevated in sepsis patients ranging from 164 to 907 ng/ml and 256.6 to 750 ng/ml, respectively [6], [7], [8]. Unfortunately, there are still some controversy about the association of MMP-9, TIMP-1, the ratio of MMP-9/TIMP-1, and mortality. Many clinical studies have reported that TIMP-1 is significantly increasing in non-surviving sepsis patients [6], [7], [8], [9], [14], [15]. While, lower MMP-9 and MMP-9/TIMP-1 ratio were found in non-surviving group [6], [7], [8], [14].

Our finding demonstrated no correlation between these three biomarkers and lactate concentration. These results are in contrast with several studies. One study showed that MMP-9 and MMP-9/TIMP-1 ratio negatively and significantly correlated with lactate concentration while TIMP-1 is positively and significantly correlated with lactate concentration [7]. A study by Lorente *et al.* also reported the same outcome where MMP-9/TIMP-1 ratio is negatively correlated with lactate concentration when measured on days 1 and 4 but not day 8 [8].

We believe that these differences may be due to our limitations in this study. First, we did not divide the patient into subgroups of surviving and non-surviving groups as we did not collect the data regarding the mortality. This could give us additional information whether the results are significantly different or not between two groups. Multiple studies have shown controversial results as mentioned above. Second, we believe that multiple measurements of MMP-9 and TIMP-1 in different timeline could show us the pattern of increasing or decreasing MMP-9 and TIMP-1 levels and could result in different findings as MMP-9 and TIMP-1 levels take time to regulate. Further research with a larger population and different settings is needed to be carried out to validate these findings.

Conclusion

This study showed no correlation between MMP-9, TIMP-1, and ratio of MMP-9/TIMP-1 toward lactate concentration.

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